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PROGRAM NMPhumPG.ACSL

!PBPK MODEL FOR N-METHYL PYRROLIDONE in pregnant women

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!First Created 8.8.08
!FINAL REPORT FROM INITIAL rat MODEL DEVELOPMENT SUBMITTED 9.02
!MODEL CONFIGURED FOR INHALATION (OPEN, WHOLE BODY/NOSE ONLY)
!   IV, ORAL,  DERMAL, AND IP  ROUTES OF ADMINISTRATION.

!MODEL TRACKS DISPOSITION OF NMP AND 5-HNMP.
!ASSUMPTIONS:
!     (1) FLOW-LIMITED (ALL COMPARTMENTS)
!     (2) METABOLISM OF NMP BY A sat PATHWAY TO FORM 5HNP
!     (3) METABOLISM OF HNP BY SATURABLE PATHWAY TO ETC.
!     (5) METABOLISM OCCURS ONLY IN THE LIVER
!     (6) TISSUE:BLOOD PART. COEFF. RAT = HUMAN = KRISHNAN EQN
!           updated in cmd file to measured in-house
!     (7) 5HNP ELIMIN FROM MIXED VENOUS - 1ST ORDER
!      THIS DIFFERS FROM 02: URINE BY *GFR CLEARANCE FROM KIDNEY
!   METAB RATE CONST. FROM REPORT - UPDATED WITH LIT VALUES in cmd file
!   Other parameters changed nominally to harmonize with fetal IPA model
of
!     Gentry et al. Regu Tox Pharm 36:51-68, 2002
! Gentry model notes:
! -Coding for pregnancy is from MeHgFat.CSL with some minor changes
! -Physiological parameters are from MeHgFat.CSL (ajusted as needed)
! -Non-pregnant mammary tissue and uterine volume is from ICRP
! -Non-pregnant mammary tissue and uterine blood flows are based on the
! - ratios of mammary and uterine tissue volumes to rapidly perfused
! - tissue volume and blood flow to rapidly perfused tissue where rapidly
! - perfused tissue includes liver, lung, etc.
! - ((VMamC/VRapC)*QRapC) and ((VUtrC/VRapC)*QRapC)
! -Data used to fit curve for growing rapidly perfused tissue in
! - MeHgFat.CSL was refit separately to fit curves for growing uterus
! - and mammary tissue in this model
! -Body weight and cardiac output are calculated as the initial values
! - plus the change in the growing compartments
! -Increase in blood flow to fat, mammary tissue, and uterus are modeled
! - as being proportional to the increase in volume in those compartments
! - based on the data in Thoresen and Wesche, 1988 (uterus and mammary
! - tissue)
!
! Further updates by Paul Schlosser, US EPA in August 2013 and September
2014


INITIAL

      table reslvl, 1, 1441 / 1441*0.0, 1441*0.0 /

! Human Total Pulmonary Ventilation Rate (L/hr for 1 kg animal)
  CONSTANT     QPC = 27.75
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! Human Blood Flows (fraction of cardiac output)
  CONSTANT     QCC = 12.9        ! Cardiac output (L/hr for 1 kg animal)
  CONSTANT   QFatC = 0.052        ! Fat (non-pregnant female)
  CONSTANT   QLivC = 0.227        ! Liver
  CONSTANT   QMamC = 0.027        ! Mammary tissue (non-pregnant female)
  CONSTANT   QRapC = 0.325       ! Rapidly perfused
  CONSTANT   QSkC = 0.058        ! Skin
  CONSTANT   QUtrC = 0.0062       ! Uterus (non-pregnant female)

! Permeability-Area Product (L/hr)
  CONSTANT    PAFC = 0.01         ! Diffusion on fetal side of placenta
from Gentry

! Human Tissue Volumes (fraction of body weight)
  CONSTANT  BWInit = 67.8        ! Pre-pregnancy body weight (kg)
  CONSTANT   VAlvC = 0.0079       ! Alveolar blood
  CONSTANT VBLC=0.06
  CONSTANT   VFatC = 0.273        ! Fat (non-pregnant female)
  CONSTANT   VLivC = 0.026        ! Liver
  CONSTANT   VMamC = 0.0062       ! Mammary tissue (non-pregnant female)
  CONSTANT   VRapC = 0.1044       ! Rapidly perfused
  !CONSTANT   VSlwC                    ! Slowly perfused is calculated
below
  CONSTANT   VUtrC = 0.0014       ! Uterus (non-pregnant female)
  CONSTANT VSKC=0.19

! Human Dermal Exposure Parameters
  CONSTANT       P = 0.0016          ! Permeability constant (Kp) (cm/hr)
  CONSTANT     PV=31.0                           ! PERMEABILITYT
CONSTANT (CM/HR) FOR VAPOR


 !FOR PARENT MODEL, SKIN COMPARTMENT IS ONLY DEFINED AS DOSED SKIN
   CONSTANT      SAl = 0.01         !SURFACE AREA EXPOSED to liquid,
SQ.CM
   CONSTANT      SAvc = 0.25         !fraction SURFACE AREA EXPOSED to
gas/vapor, SQ.CM
   CONSTANT HT=170.0         !height (or length) of reference man
     TSA = 71.81*(BWinit**0.425)*(HT**0.725)  !for humans, DuBois and
DuBois, 1916, as reported in Reference Man
           SAv = SAVC*TSA         ! SURFACE AREA EXPOSED to gas/vapor,
SQ.CM
      VSKlC = VSKC*SAl/TSA
      QSKlC = QSKC*SAl/TSA
      VSKvC = VSKC*SAv/TSA
      QSKvC = QSKC*SAv/TSA

CONSTANT FAD = 0.0  !FRACTION ABSORBED - FROM BADER ET AL, CALCULATE FROM
AMNT REMAINING ON GAUZE
 CONSTANT PVL=0.0

  ! Slowly perfused (defined as balance of tissues and flows)
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   VSlwC = 0.91 - ( VFatC + VLivC + VMamC + VRapC + VUtrC + VSKvC +
VSKlC)
       ! NOTE: 0.91 IS APPROX WHOLE BODY LESS BONE
   VSLwC5=0.91 - (VFatC + VLivC + VRapC)
    QSlwC = 1.0 - (QFatC + QLivC + QMamC + QRapC + QUtrC + QSKvC + QSKlC)
   QSlwC5 = 1.0 - (QFatC + QLivC + QRapC)

! Molecular Weights
  CONSTANT  MW=99.13      !MOL. WT. NMP, MG/MMOL
 CONSTANT  MW1= 116.14     !MOL. WT. 5-HNP, MG/MMOL

     Stoch = MW1/MW

! Human NMP/Blood Partition Coefficients
!EXPERIMENTALLY MEASURED RATVALUES
  CONSTANT    PB = 450.0        ! Blood/air
  CONSTANT    PFat = 0.61         ! Fat
  CONSTANT    PLiv = 1.00         ! Liver
  CONSTANT    PMam = 1.0          ! Mammary tissue, estimated from liver
  CONSTANT    PPla = 0.31         ! Placenta
  CONSTANT    PRap = 1.0         ! Rapidly perfused tissue, liver
  CONSTANT    PSlw = 0.30         ! Slowly perfused tissue, muscle
  CONSTANT    PUtr = 0.34         ! Uterus
  CONSTANT    PSKA = 44.5           ! use (blood/air)*(rat
skin:liquid)/(human blood:liquid)
  CONSTANT    PSKL = 0.42     ! MEASURED SKIN;LIQUID (rat)
     constant         pskb = 0.099     ! (rat skin:liquid)/(human
blood:liquid)
  CONSTANT    PLU= 0.1         ! LUNG:BLOOD

!METABOLIC RATE CONSTANTS
!**THESE ARE FROM PAYAN ET AL
  !NMP TO 5HNP
           CONSTANT Af1 = 0.0112 ! AFFINITY CONSTANT, l/MG
           CONSTANT VK1C = 0.4663 ! Vmaxc/Km, 1/(hr * BW^0.75 )

! Human 5HNMP volume of distribution
      CONSTANT VOD5Hc = 0.3  ! VOLUME-OF-DISTRIBUTION
           VOD5H = VOD5Hc*BWinit
  !No fetal compartment for metabolite, NMP is considered the active
moiety

!5HNP TO OTHER METABS
    ! CONSTANT  KM2=22.8          !MICHAELIS CONSTANT, MG/L
    ! CONSTANT  VMAX2C=1.0        !MAX. ENZ. ACT., MG/HR/L
    CONSTANT VK2C=0.0326    ! VMAX2C/KM2, since clearance ~ liner
1/(hr*kg^0.75)
! Human Uptake and Clearance Parameters
  !URINARY ELIMINATION OF 5-HNMP - CLEARED FROM BLOOD
  !note first order rate commented out, saturable fits better
     CONSTANT KAS=5.0
    CONSTANT  KME=3.83      !First-order constant for 5HNMP in urine
(L/hr)
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    CONSTANT KUMNE=0.182                !First-order CONSTANT FOR NMP IN
URINE (L/hr)

! Initialize Human Concentrations in Tissues (mg/L)
  CONSTANT   ICArt = 0.0          ! Blood
  CONSTANT   ICFat = 0.0          ! Fat
  CONSTANT   ICLiv = 0.0          ! Liver
  CONSTANT   ICRap = 0.0          ! Rapidly perfused
  CONSTANT   ICSkn = 0.0          ! Skin
  CONSTANT   ICSlw = 0.0          ! Slowly perfused
     ICMam = ICSlw                ! Mammary tissue
     ICUtr = ICRap                ! Uterus

! Dosing Parameters
  CONSTANT    Concppm = 0.0          ! Inhaled concentration (ppm)
  CONSTANT   CONCMGM = 0.0                    ! Inhaled concentration
(mg/m3)
  CONSTANT  IVDose = 0.0          ! IV dose (mg/kg)
  CONSTANT   PDose = 0.0          ! Oral dose (mg/kg)
      constant PDose2=0.0
      constant PDose3=0.0
  CONSTANT  PDrink = 0.0          ! Drinking water dose (mg/kg/day)
  CONSTANT   TChng = 24.0         ! Length inh. exposure or IV inj.(hrs)
  CONSTANT  DaysWk = 5.0          ! Number of exposure days per week
  CONSTANT    TMax = 24.0         ! Maximum time for exposures
CONSTANT s2=0.0
      !INHALATION ON
CONSTANT p2=3.0
      !INHALATION EXPOSURE
CONSTANT S3=3.16                                                !INHALTION
RESUME (HANOVER STUDY)
CONSTANT P3=3.0
      !SECOND DAILY EXPOSURE PERIOD
constant on3=1.0 ! Set to zero to turn off 2nd daily pulse;
constant fullweek=168.0     ! hrs in a fullweek
hrsweek=24.0*DaysWk    ! hrs/week in workplace

! STARTDS IS ADDED TO TCHNG TO ALLOW FOR DOSING THAT DOES NOT START AT
T=0
!INITIAL EXPOSURE CONDITIONS
 !DERMAL
      CONSTANT CONCL = 0.0       !CONC OF NMP IN LIQUID, MG/L
                constant srate = 0.0              ! mg/hr delivered to
skin by spray application
      CONSTANT VLIQ0 = 1.0e-99     !INITIAL VOLUME APPLIED, L
      CONSTANT DENSITY=1.02e6     !     Density (mg/L) @ 40C, ~ skin
temperature
          CONSTANT RESID=0.0          !AMOUNT STICKING TO EXPOSURE
SYSTEM, MG
                constant BRUSH=0.0                ! Set to 1.0 for
brush/liquid exposure
      DDN = (CONCL - 1.0)*VLIQ0*FAD ! Subtract 1 mg/L, ~ 1 ppm, from
initial conc. to avoid VLIQ --> 0
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                AH20 = (DENSITY+1.0-CONCL)*VLIQ0 ! ... and add it to
H20.
! Note, for application of 100% NMP, it is not possible for CSURF to drop
below 100%.
! 100% NMP is not diluted in anything, so the "solution" can't become
less dilute.
! The volume (VLIQ) would actually decrease until it's all absorbed.
! Unless the experiment runs long enough for 100% absorption, treat VLIQ
as
! extremely large, ~ 10^9, for 100% NMP.
! But check that you don't predict more absorption than was actually
applied!


       !IN VITRO HUMAN VAN DYK ET AL. AIHA J 56: 651-660
        !START WITH SMALL SA SO VSKE IS NON-ZERO (USED IN DENOMINATOR OF
CSK CALCULATION)


  ! Exposure Conditions Based on User Defined Initial Amounts of Chemical
(mg)
     IF (concppm.EQ.0.0) THEN
     concmg=concmgm/1000.0                                  !CONCERT MG/M3
to mg/L
  ELSE
       CONCmg = CONCppm*MW/24451.    !Convert ppm to mg/Liter!
  ENDIF

!CONSTANT CONCMG=0
      !HANNOVER STUDY UNIT MG/M3 SO CONCMG /1000(l/M3)
CONSTANT   DOSEINTERVAL=24.0                          !TIME BETWEEN DAILY
DOSES

! Simulation Control Parameters
  CONSTANT StartDs = 0.0          ! Time first dose is given (hrs)
  CONSTANT   TStop = 6480.0       ! Run simulation for about 9 months
  CONSTANT   CIntC = 0.1
      CONSTANT   GDstart = 0.0          ! Gestation day on which
simulation starts

! Scaled Human Pulmonary Ventilation Rate (L/hr)
        QP = QPC * (BWInit**0.75)
      QAlv = 0.67 * QP

! Scaled Human Blood Flows (L/hr)
    QCInit = QCC * (BWInit**0.75)
    QFatI = QFatC * QCInit
    QLiv = QLivC * QCInit
    QMamI = QMamC * QCInit
           QPlaI = 58.5 * VPlaI   ! value for 'days'=0 per calculation
below
    QRap = QRapC * QCInit
    QSlw = (QSlwC * QCInit) - QPlaI
    QUtrI = QUtrC * QCInit
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    QSkl = QSKlC * QCInit
    QSkv = QSKvC * QCInit


! Scaled Human Tissue Volumes (L)
      VAlv = VAlvC * BWInit
      VFatI = BWInit*(VFatC+(0.09*exp(-12.90995862*exp(-
0.000797*24.0*GDstart))))
      VFetI = 3.50 * (exp(-16.081*exp(-5.67e-4*24.0*GDstart))+ exp(-
140.178*exp(-7.01e-4*24.0*GDstart)))
      VMamI = BWInit*(VMamC+(0.0065*exp(-7.444868477*exp(-
0.000678*24.0*GDstart))))
      VPlaI = 0.85*exp(-9.434*exp(-5.23e-4*24.0*GDstart))
      VUtrI = BWInit*(VUtrC+(0.02*exp(-4.715669973*exp(-
0.000376*24.0*GDstart))))
      VLiv = VLivC * BWInit
      VRap = VRapC * BWInit
     VSKl = VSKlC * BWinit
     VSKv = VSKvC * BWinit
       VBL=VBLC * BWINIT
       VSlw = (VSlwC * BWInit)

! Scaled Human Metabolism Parameters
                      VK1 = VK1C * (BWInit**0.75)
           VK2 = VK2C * (BWInit**0.75)
! Initialize Human NMP Amounts in Tissues
     IAArt = ICArt * VAlv
     IAFat = ICFat * VFatI
     IALiv = ICLiv * VLiv
     IAMam = ICMam * VMamI
     IARap = ICRap * VRap
     IASkl = ICSkn * VSKl
     IASkv = ICSkn * VSKv
     IASlw = ICSlw * VSlw
     IAUtr = ICUtr * VUtrI
   InitTot = IAArt + IAFat + IALiv + IAMam + IARap + IASkl + IASkv +
IASlw + IAUtr


! Initialize Starting Values
        BW = BWInit
     Drink = (PDrink * BW) / 24.0      ! Drinking water dose (mg/hr)
      CINT = CIntC
        IV = 0.0
    DayExp = 1.0
      CInh = 0.0
     CONSTANT  FRACIN = 0.97     !FRACTIONAL UPTAKE OF NMP BY INHAL,START
AT 65%
                                        !of alveolar - as in Akesson et
al 1997
    CONSTANT  FRACOR = 1.0      !FRACTION ABSORBED ORALLY, INITALLY 100%

! Convert oral dose from ug/kg to umoles
! Modify dose to account for fractional absorption
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ODOSE1= PDOSE * BW * FRACOR    ! umoles
ODOSE2= PDOSE2* BW * FRACOR    ! umoles
ODOSE3= PDOSE3* BW * FRACOR    ! umoles

CONSTANT TIME=0.0
CONSTANT TIME1 = 0.0  ! !'daily rat expo (hr)'
CONSTANT TIME2 = 4.0  ! !'SECOND DAILY EXPOSURE (hr)'
CONSTANT TIME3 = 4.0  ! !'THIRD DAILY DOSE'
CONSTANT REPTM=720.0   ! CHANGE TO 24 FOR DAILY DOSING

SCHEDULE DOSE1 .AT. TIME1

DZONE = 1.0 ! Start with exposure on
schedule offd.at.p2
schedule OND2.at.24.0
if (ON3) schedule OND3.at.s3

END                ! End of Initial


DYNAMIC
  ALGORITHM  IALG = 2             ! Gear stiff method

 DISCRETE DOSE1
 ODOSE = ODOSE+ODOSE1
 SCHEDULE DOSE2 .AT. (TIME+TIME2)
 END

 DISCRETE DOSE2
 ODOSE = ODOSE+ODOSE2
 SCHEDULE DOSE3 .AT. (TIME+TIME3)
 END

 DISCRETE DOSE3
 ODOSE = ODOSE+ODOSE3
 SCHEDULE DOSE1 .AT. (TIME+REPTM-TIME2-TIME3)
 END

DISCRETE DoseOn    ! Start dosing
  INTERVAL DoseInt = 24.0         ! Interval to repeat dosing
  SCHEDULE DoseOff .AT. T + TChng
  IF ((T.GE.StartDs) .AND. (T.LT.TMax)) THEN
           IF (T.LE.(StartDs+TChng)) THEN
                IF (IVDose.GT.0.0) CINT = MIN(CIntC, (TChng/10.0))
      IV = (IVDose*BW) / TChng    ! Rate of intravenous dosing (mg/hr)
           ENDIF
     ENDIF
END ! DoseOn

DISCRETE DoseOff
  CInh = 0.0
  CINT = CIntC
  IV = 0.0
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END

discrete OND2
      DZONE=1.0
      SCHEDULE OND2.AT.(T+24.0)
      SCHEDULE OFFD.AT.(T+P2)
END

discrete OND3
      DZONE=1.0
      SCHEDULE OND3.AT.(T+24.0)
      SCHEDULE OFFD.AT.(T+P3)
END

!EXPOSURE CONTROL
DISCRETE OFFD
      DZONE=0.0   !TURN OFF DERMAL
END

DERIVATIVE
     Hours = T
   Minutes = T * 60.0
      Days = T / 24.0 + GDstart
           Gtime = T + GDstart*24.0

! Volume of human fat (L)
      VFat = BWInit*(VFatC+(0.09*exp(-12.90995862*exp(-0.000797*Gtime))))

! Volume of human fetus (L)
      VFet = 3.50 * (exp(-16.081*exp(-5.67e-4*Gtime))+ exp(-140.178*exp(-
7.01e-4*Gtime)))

! Volume of human mammary tissue (L)
      VMam = BWInit*(VMamC+(0.0065*exp(-7.444868477*exp(-
0.000678*Gtime))))

! Volume of human placenta (L)
      VPla = 0.85*exp(-9.434*exp(-5.23e-4*Gtime))

! Volume of human uterus (L)
      VUtr = BWInit*(VUtrC+(0.02*exp(-4.715669973*exp(-0.000376*Gtime))))

! Increase in human body weight (kg)
        BW = BWInit + (VFat - VFatI) + VFet + (VMam - VMamI) + VPla +
(VUtr - VUtrI)

! Scaled human alveolar ventilation (L/hr)
        QP = QPC * (BW**0.75)
      QAlv = 0.67 * QP

! Increase in human blood flows (L/hr)
      QFat = QFatI * (VFat / VFatI)
      QMam = QMamI * (VMam / VMamI)
      QUtr = QUtrI * (VUtr / VUtrI)
```

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! Human Blood flow to placenta (L/hr)
      QPla = 58.5 * VPla

! Increased human cardiac output (L/hr)
       QC = QCInit + (QFat - QFatI) + (QMam - QMamI) + (QPla - QPlaI) +
(QUtr - QUtrI)
                 QSlw5 = Qc - (QFat + QLiv + QRap)
                 VSlw5 = BW - (VFat + VLiv + VRap)

! Scaled permeability-area product
       PAF = PAFC * (VFet**0.75)


! ------------------ HUMAN NMP MODEL -------------------------

! Amount Exhaled (mg)
     RAExh = QAlv * CAlv
      AExh = INTEG(RAExh, 0.0)

CI = concmg*czone + RESLVL(T)
! for a 5 day/wk exposure, change first pulse to pulse(0,7*24,5*24)
! for daily, pulse(0,1e6,24)

           TORAL= ODOSE1 - AO          !AMT ABSORBED ORALLY, MG!
RSTOM = -KAS*AO
RAO = KaS*AO    ! Change in stomach (umole/hr)
AO=ODOSE1+INTEG(Rstom,0.0)    ! Amt in stomach (umole)

! Amount in Fat (mg)
     RAFat = QFat * (CArt - CVFat)
      AFat = INTEG(RAFat, IAFat)
      CFat = AFat / VFat
     CVFat = CFat / PFat

! Amount in Fetus (mg)
     RAFet = PAF * (CPla - CFet)
      AFet = INTEG(RAFet, 0.0)
      CFet = AFet / VFet
   AUCCFet = INTEG(CFet, 0.0)

! Amount in Liver (mg)
     RALiv = (QLiv * (CArt - CVLiv)) + RAO + Drink - RAMet1
      ALiv = INTEG(RALiv, IALiv)
      CLiv = ALiv / VLiv
     CVLiv = CLiv / PLiv

! Amount Metabolised in Liver -- Saturable (mg)
    RAMet1 = VK1 * CVLiv / (1 + af1*CVLiv)
     AMet1 = INTEG(RAMet1, 0.0)

! Amount in Mammary Tissue (mg)
     RAMam = QMam * (CArt - CVMam)
      AMam = INTEG(RAMam, IAMam)
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      CMam = AMam / VMam
     CVMam = CMam / PMam

! Amount in Placenta (mg)
     RAPla = (QPla * (CArt - CVPla)) + (PAF * (CFet - CPla))
      APla = INTEG(RAPla, 0.0)
      CPla = APla / VPla
     CVPla = CPla / PPla

! Amount in Rapidly Perfused Tissue (mg)
     RARap = QRap * (CArt - CVRap)
      ARap = INTEG(RARap, IARap)
      CRap = ARap / VRap
     CVRap = CRap / PRap

!ASKl = AMOUNT NMP IN liquid-exposed SKIN TISSUES (MG) AND DERMAL DOSING
(from vapor)
! Liquid exposure when czone = 1, otherwise czone = 0. CI = air
concentration
czone = pulse(0.0,fullweek,hrsweek)*DZONE
! for a 5 day/wk exposure, use fullweek=7*24, hrsweek=5*24 (Dayswk=5)
! for a single day, fullweek=1e16, hrsweek=24 (Dayswk=1)

RADL = (PVL*SAL/1000.0)*(CSURF - (CSKL/PSKL))*czone*BRUSH
  ! Net rate of delivery to "L" skin from liquid, when liquid is there
      ADLL = integ(RADL, 0.0)
RADVL = (PV*SAL/1000.0)*(CI - (CSKL/PSKA))*(1.0-Czone)
 ! Net rate of delivery to "L" skin from air, when liquid not present
      ADVL = integ(RADVL, 0.0)
ASURF = INTEG(-RADL, DDN) ! Aount in liquid.  DDN is the initial amount.
VLIQ = (AH20 + ASURF)/DENSITY
CSURF = ASURF/VLIQ

RASKL = QSKL*(CArt - CvSKL) + RADL + RADVL  ! Rate of change in "L" skin
compartment
ASKL = INTEG(RASKL, 0.0)     ! Amount in "L" skin
CSKL = ASKL/VSKL                  ! Concentration in "L" skin
CvSKL = CSKL/PSKB                 ! Concentration in venous blood exiting
"L" skin


!ASKv = AMOUNT NMP IN vapor-exposed SKIN TISSUES (MG) AND DERMAL DOSING
(from vapor);
! "SKv" (vapor-only-exposed) skin compartment.  CI = air concentration

RADVv = (PV*SAv/1000.0)*(CI - (CSKv/PSKA))   ! Net rate of transfer from
air to skin
       ADVv = INTEG(RADVv,0.0)     !'AMT NMP ABSORBED DERMAL,MG'
RASKv = QSKv*(CArt - CvSKv) + RADVv  ! Rate of change in "V" skin
ASKv = INTEG(RASKv, 0.0)           ! Amount in "V" skin
CSKv = ASKv/VSKv                    ! Concentration in "V" skin
CvSKv = CSKv/PSKb                  ! Concentration in venous blood
exiting "V" skin
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! Amount in Slowly Perfused Tissue (mg)
     RASlw = QSlw * (CArt - CVSlw)
      ASlw = INTEG(RASlw, IASlw)
      CSlw = ASlw / VSlw
     CVSlw = CSlw / PSlw

! Amount in Uterus (mg)
     RAUtr = QUtr * (CArt - CVUtr)
      AUtr = INTEG(RAUtr, IAUtr)
      CUtr = AUtr / VUtr
     CVUtr = CUtr / PUtr

! BLOOD VENOUS ARTERIAL (c)
CVEN=(QFAT*CVFat + QLIV*CVLiv + QMAM*CVMam + QPLA*CVPla + QRap*CVRap +
QSlw*CVSlw &
           + QUtr*CVUtr + QSKV*CVSKv + QSKL*CVSKL + IV) / QC
ivtot=INTEG(IV, 0.0)

! Amount in Arterial Blood (mg)
      RAINH = QAlv*(CI*FRACIN - CAlv)
     RABld = RAINH + QC*(CVen-CArt) - RAUNP
      INhaltot = INTEG(RAINH, 0.0)
      ABld = INTEG(RABld, IAArt)
      CArt = ABld / VBL
      CAlv = CArt / PB
   CAlvPPM = CAlv * 24450.0 / MW
   AUCCBld = INTEG(CArt, 0.0)

! Amount in Urine (mg)
   RAUNP = KUMNE*CART              !FIRST ORDER RATE OF LOSS (URINE
      AUNP = INTEG(RAUNP,0.0)

! -------------------- HUMAN 5HNMP MODEL --------------------------

! Amount in body (mg)
    RA5H = (RAMet1*STOCH) - RAMetM1 - RAUHP
     A5H = INTEG(RA5H, 0.0)
     Cven1 = A5H / VOD5H

! Amount Metabolised [in Liver] -- Saturable (mg)
           RAMetM1 = VK2*Cven1
    AMetM1 = INTEG(RAMetM1, 0.0)

! Amount in Urine (mg)
   RAUHP = KME*Cven1
AUHP = INTEG(RAUHP,0.0)

! ----------------- CHECK MASS BALANCE ------------------------------
  INTOT=INTEG((QAlv*CI*FRACIN), 0.0)

   TDose = INTOT  + AO + InitTot+TORAL+ADLL+ADVL+ADvV
   NMPTOT = ABld + AFat + AFet + ALiv + AMam + APla + ARap + ASkl + ASkv
+ ASlw + AUtr + AExh + AUnp + AMET1
      MassBal = TDose/(NMPTOT+0.000000000001)
```

```
TERMT(T.GT.TSTOP, 'Simulation Finished')

END                ! End of Derivative

TERMINAL
   DAUCCBld = AUCCBld * 24.0 / TStop
   DAUCCFet = AUCCFet * 24.0 / TStop
END

END                ! End of Dynamic
END                ! End of Program
```